REMARKS

Claims 1, 16 and 23 have been amended. Claims 15, 17 and 19 have been canceled without prejudice or disclaimer. Claims 18 and 20-21 and claims 11-14 and 22 were previously withdrawn or canceled, respectively. Subsequent to the entry of the present amendment, claims 1-10, 16 and 23-25 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

I. Amendments to the Claims

Claim 1 has been amended to recite a dosage. The amendment is supported in the application, for example, Example 21 describes the effect of bikunin on tracheal mucus velocity (TMV) in sheep (pages 80-81 of the specification). Bikunin was delivered to sheep airways using a Raindrop jet nebulizer filled with 3mL of 3mg/mL stock (or about 9mg total). Tracheal mucus velocity was measured at different time periods up to 8 hours. TMV was increased as compared to the same time points in animals receiving PBS, or a no-bikunin control. Example 21 also describes that a lower dose, a dose less than 9mg, did not result in any significant increase in TMV between treatment and control groups. Thus, the minimum dosage in order to observe any significant TMV is at least 9mg. Example 21 describes SEQ ID NO:52 (1-170), which one skilled in the art would accept as reasonably predictive of the claimed SEQ ID NO:8 (1-92); as discussed in more detail below.

Claims 16 and 23 have been amended to improve their form, e.g., to correct claim dependency or to provide for antecedent basis of a subsequent claim.

Claims 15, 17 and 19 have been canceled, in part, as suggested by the Office Action, because they do not further limit claim 1 from which they depend.

No new matter has been added.

II. Rejections under 35 U.S.C. §112, First Paragraph (written description)

Claims 23-25 are rejected under 35 U.S.C. §112, first paragraph for allegedly failing to describe in the specification in such a way as to reasonably convey to one skilled in the art that the Applicant, at the time of filing, had possession of the claimed invention. This is a new matter rejection. Applicant traverses this rejection as it may apply to the pending claims.

According to the Office Action states (page 3 and 4):

> MPEP §2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description". Applicant points to Examples 17-26 at pp. 71-85 of the specification as showing support for the recited limitations of claims 23-25. However, the recited claim limitations go beyond the subject matter originally filed.Examples 17-26 teach purification of placental Bikunin (1-170) from cultured CHO cells and measuring various effects of placental Bikunin (1-170) on cultured mammalian cells, sheep, and guinea pigs. The species of cultured mammalian cells, sheep, and guinea pigs fails to support the genus of subjects as recited in claim 1. Even assuming arguendo the species supported the broader genus, the examiner can find no teaching wherein SEQ ID NO:8 inhibits sodium channels, inhibits epithelial sodium channels, and/or increases TMV.

It is submitted that MPEP §2164.03 is clear with regards to what one skilled in the art would accept as being "predictable" at the time of the filing of the application (emphasis added):

> ..."predictability or lack thereof" in the art refers to the ability of one skilled in the art to *extrapolate the disclosed or known results to the claimed invention.* If *one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art.* On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

> [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

In brief, the Office Action alleges that the activity of SEQ ID NO:52 (1-170) in the present application is allegedly not predictive of the activity of SEQ ID NO:8 (1-92) of the claimed invention. Therefore, according to the Office Action, there is no alleged support for the claimed activity being associated with the claimed bikunin polypeptide, or SEQ ID NO:8 (1-92)

Applicants submit that one skilled in the art would accept that the protease inhibitory activity of SEQ ID NO:52 (1-170) is reasonably predictive of the protease inhibitory activity of SEQ ID NO:8 (1-92) for the following reasons.

First, SEQ ID NO:8 (1-92), SEQ ID NO:4 (7-64) and SEQ ID NO:52 (1-170) described in the present invention all include the entire first Kunitz-domain (or KID-1; see FIG.4 of the application), which contains a set of 6 conserved cysteine residues. The Kunitz-domain confers protease inhibitory activity to the bikunin polypeptides. In fact, Tamburini describes protease inhibitory activity for various bikunin polypeptides, including SEQ ID NO:4 (7-64) and SEQ ID NO:52 (1-170). For example, Table 4A and 4B and Table 9 describe dissociation constants (Ki) of SEQ ID NO:4 (7-64) and SEQ ID NO:52 (1-170), respectively. Table 4 shows that the low Ki values for SEQ ID NO:4 (7-64) are comparable to the Ki values in Table 9 for SEQ ID NO:52 (1-170). Low Ki values indicate higher affinity between bikunin and bikunin substrates resulting in greater protease inhibitory activity. So, SEQ ID NO:4 (7-64) is as effective a protease inhibitor as SEQ ID NO:52 (1-170). Thus, one skilled in the art would accept that the inhibitory

activity of SEQ ID NO:52 (1-170) as described in Examples 18, 21-24 and 26 are reasonably predictive of SEQ ID NO:4 (7-64). Further, since SEQ ID NO:4 (7-64) and SEQ ID NO:8 (1-92) are structurally similar, one skilled in the art would accept that any activity imputed to SEQ ID NO:4 (7-64) would be imputed to SEQ ID NO:8 (1-92). Hence, one skilled in the art would accept that SEQ ID NO:8 (1-92) would operate as alleged. Therefore, Applicants were in possession of the claimed invention at the time of filing and SEQ ID NO:8 (1-92) can be reasonably predicted to have the claimed activity, e.g., inhibiting sodium channels, inhibiting epithelial sodium channels, and/or increasing TMV.

Accordingly, withdrawal of rejection of claims 23-25 under 35 U.S.C. §112, first paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §103

Claims 1-10, 15, 19 and 20 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Tamburini et al. (WO97/33996) in view of Rasche et al. and O'Riordan et al. (hereinafter, "Tamburini", "Rasche," and "O'Riordan," respectively). The rejection is moot with regards to canceled claims 15 and 19. Applicants respectfully traverse this rejection as it may apply to the pending claims.

According to the Office Action, the prior art allegedly suggests a method of increasing the rate of mucociliary clearance as recited the claimed invention. Further, according to the Office Action (page 7):

> ... the claimed invention only requires administering an effective mucociliary clearance stimulatory amount of a composition comprising SEQ ID NO:8, thereby accelerating mucociliary clearance, which is taught by the combination of references. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claimed invention describes that Kunitz-type inhibitors accelerate the rate of mucocilliary clearance by inhibiting sodium channels and

> affecting the potential difference, thereby increasing the TMV) are not recited in rejected claim(s) 1-10,15-17, and 19. ... Furthermore, although claims 23-25 limit the activity of the inhibitor to inhibiting sodium channels, optionally wherein the sodium channel is an epithelial sodium channel or to increasing TMV in the subject, absent evidence to the contrary, these are inherent features of the peptide of Tamburini et al. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. See MPEP 2112. The peptide of SEQ ID NO:8 is taught by Tamburini et al. and the administration of this peptide for accelerating mucocilliary clearance in a subject is taught by the combination of references.

To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) a reasonable expectation of success; and 3) the references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143.

Claim 1 has been amended and is supported in the application as discussed above. Claim 1 recites that an effective amount SEQ ID NO:8 is "at least about 9mg", which dosage is described in Example 21.

First, the discussion regarding SEQ ID NO:52 (1-170) and SEQ ID NO:4 (1-64) being reasonably predictive of the claimed activity of SEQ ID NO:8 (1-92) applies here. That is, one skilled in the art would accept that the activity of SEQ ID NO:4 (1-64) is a potent protease inhibitor similar to SEQ ID NO:52 (1-170), thus the activity of SEQ ID NO:52 as described in the Examples, in particular, Example 21, is reasonably predictive of the function of SEQ ID NO:4 (1-92). Further, since SEQ ID NO:4 (7-64) and SEQ ID NO:8 (1-92) are structurally similar, one skilled in the art would accept that any activity imputed to SEQ ID NO:4 (7-64) would be imputed to SEQ ID NO:8 (1-92). Therefore, one skilled in the art would accept that

the activity of SEQ ID NO:52 (1-170) as described in Example 21, is reasonably predictive and can be imputed to the activity SEQ ID NO:8 (1-92); and SEQ ID NO:8 (1-92) would operate as alleged.

Based on the above, it is submitted, that Tamburini alone does not establish a *prima facie* case of obviousness. Tamburini only discloses that bikunin polypeptides are potent protease inhibitors as described in Tables 3-9 and Examples 1-10. Tamburini does not teach or suggest the claimed invention, in particular, the claimed dosage of the claimed bikunin polypeptide. Obviousness also requires a reasonable expectation of success. *In re Merck & Co., Inc.* 800 F.2d 1091, 231, USPQ 375 (Fed. Circ. 1986); MPEP §2143.02. However, Tamburini does not teach or suggest that bikunin effects mucociliary clearance at *any* dosage, so there can be no reasonable expectation of success in modifying Tamburini to make or produce the claimed invention. Lastly, obviousness requires that all the claimed limitations be taught or suggested. Again, since Tamburini does not teach or suggest *any* dosage to affect mucociliary clearance at all, Tamburini cannot be said to teach or suggest all the claimed limitations, including the claimed dosage. Thus, there is no case of *prima facie* obviousness with regards to Tamburini alone.

It is further submitted that there is no case of *prima facie* obviousness with regards to Tamburini in view of Rasche and O'Riordan, because Rasche and O'Riordan do not teach or suggest the claimed invention either. Tamburini only discloses that bikunin polypeptides are potent protease inhibitors as described in Tables 3-9 and Examples 1-10. Tamburini does not teach or suggest the claimed invention, in particular, the claimed dosage of the claimed bikunin polypeptide. However, Rasche and O'Riordan do not cure the deficiencies of Tamburini. Rasche discloses the therapeutic affects of aprotinin, e.g., up to 2 Million IU/day of aprotinin inhibited sputum proteases (page 7, first paragraph; and page 8, last paragraph of the English translation of Rasche). Yet, Tamburini already demonstrated that bikunin is a more potent

inhibitor than aprotinin as shown in Tables 3-9 and Examples 1-10 of the application. Thus, one skill in the art would not look to Rasche to modify the teachings of Tamburini, since the effective dosage of bikunin as compared to aprotinin would not be the same. O'Riordan discloses that agents having anti-elastase activity may be beneficial in blocking mucociliary impairment. However, there is no teaching or suggestion in O'Riordan of *any* effective amount of these agents which would result in a mucociliary clearance. Hence, Tamburini, alone or combined, with Rasche and/or O'Riordan do not teach or suggest the claimed invention, as none of the references teach or suggest an effective mucociliary clearance stimulatory amount. Thus, in the absence of *any* suggestion or motivation in Tamburini, Rasche and/or O'Riordan, and there being no reasonable expectation of success, it cannot be said that Tamburini, alone or combined, with Rasche and O'Riordan teach or suggest all the claim limitations.

Accordingly, withdrawal of rejection of claims 1-10, 15, 19 and 20 under 35 U.S.C. §103(a) is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

A check in the total amount of $1,520.00 is enclosed as payment for the three-month extension of time fee ($1,020.00) and the Notice of Appeal fee ($500.00) for large entity. No other fees are deemed necessary in connection with this submission, however if any other fees are due, please charge any fees, or make any credits, to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

Date: August 7, 2006

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